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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/887,540	06/21/2001	Robert Klein	R-193	5814

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EXAMINER
WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
1632	

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41

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)	
09/887,540	KLEIN, ROBERT	
Examiner	**Art Unit**	
Michael C. Wilson	1632	

Offic Action Summary

-- Th MAILING DATE of this communication appears on the cover sheet with th c rrespondence address --

Peri d f r R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *1-4 and 13-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

DETAILED ACTION

The amendment to Fig. 3B has been entered. Applicants did not file a new Fig. 3A which still does not have a SEQ ID NO. If 3A is the beginning of the sequence and 3B is the end of the sequence, clarification is required either in the drawings or the description of the drawings.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. **The sequence in Fig. 3A does not have a SEQ ID NO**. Applicants must file a "Sequence Listing" accompanied by directions to enter the listing into the specification as an amendment. Applicant also must provide statements regarding sameness and new matter with regards to the CRF and the "Sequence Listing." The instant office action is made as a means of expediting prosecution; however, failure to fully comply with the sequence rules in response to the instant office action will be considered non-responsive.

Election/Restrictions

Applicant's clarification regarding claims 13-16 is acknowledged. Group VI should have been claims 13-15 and Group VII should have been claim 16.

Applicant's election with traverse of Group IV, claims 8 and 10 in Paper No. 10 is acknowledged.

Groups III (claims 5-7, 9) and V (11, 12) have been recombined with Group IV (8, 10).

Applicant argues that the constructs of Groups I and II have varying scopes but both comprise an LPR5 gene. Applicant's argument is not persuasive. Claim 4 requires two sequences homologous to an LPR5 gene with a marker gene in between which cannot encode LPR5 while claim 1 requires two sequences homologous to an LPR5 gene, which does encompass DNA encoding LPR5. LPR5 knockout constructs and constructs encoding LPR5 are different because they have different structures and different functions. The LPR5 knockout construct does not require the entire LPR5 gene while a construct encoding LPR5 requires the entire LPR5 gene. A search for a construct encoding LPR5 would not result in finding a construct having two LPR5 sequences with a marker sequence in between. A search for a construct having two LPR5 sequences with a marker sequence in between would not necessarily result in finding a construct having the entire LPR5 gene.

Applicant argues that a search of the construct of Group I would produce the cells of Group III and vice versa. Applicant's argument is not persuasive. The cells of Group III do not encode LPR5 and have a knockout construct while the construct Group I causes expression of LPR5 and cannot have a selection marker in-between the two LPR5 sequences as in claim 4.

Applicant argues a search of Groups I and IV or V would not be undue. Applicant's argument is not persuasive because the construct encodes LPR5 while the transgenics do not have a construct that encodes LPR5. In fact, the transgenics have a disruption in LPR5.

Applicant argues a search of Groups I and VI would not be undue. Applicant's argument is not persuasive because the construct encodes LPR5 while the cells used in the method have a disruption in LPR5 and do not have a construct encoding LPR5.

Applicant argues a search for the construct of Group I and the modulator of Group VII would not be undue. Applicant's argument is not persuasive because they are materially distinct products. The search for each is mutually exclusive.

Applicant argues a search for the LPR5 knockout construct (Group II) and the search for cells having a disruption in LPR5 (Group III), transgenics having a disruption in LPR5 (Group IV) or methods of using the transgenics or cells (Groups V and VI) would not be undue. Applicant's argument is not persuasive. The construct has a different structure and function than the cells or transgenics. A search for the construct does not necessarily result in finding the cells or transgenics. A search for the construct does not necessarily result in finding the steps of the methods. The construct has materially distinct uses, i.e. to make transgenics or to make cells *in vitro* for testing compounds. Therefore, Group II is patentably distinct from Groups III, IV, V or VI.

Applicant argues a search for the LPR5 knockout construct of Group II and the modulator of Group VII would not be undue. Applicant's argument is not persuasive

because they are materially distinct products. The search for each is mutually exclusive.

Applicant argues a search for cells having a disruption in LPR5 (Group III), transgenics having a disruption in LPR5 (Group IV) or methods of using the transgenics to test compounds (Group V) combined with a search for methods of using the cells to test compounds (Group VI) would not be undue. Applicant's argument is not persuasive. The cells have materially distinct uses, i.e. to make transgenics or to test compounds in vitro. The construct has a different structure and function than the cells or transgenics. A search for the cells or transgenics does not necessarily result in finding the steps of the method of testing compounds using cells. A search for the method of using transgenics does not necessarily result in finding the steps of methods of using the cells in vitro. Therefore, Groups III, IV and V are patentably distinct from Group VI.

Applicant argues a search for cells having a disruption in LPR5 (Group III), transgenics having a disruption in LPR5 (Group IV), methods of making the transgenics (Group IV) or methods of using the transgenics to test compounds (Group V) combined with a search for the modulator of Group VII would not be undue. Applicant's argument is not persuasive. Cells or transgenics are materially distinct from modulators and require different searches, which are mutually exclusive. The search for the method of using transgenics to test compounds does not necessarily result in finding compounds that modulate LPR5 function. The compounds encompassed by Group VII have different uses depending upon their structure.

Applicant argues a search for the method of using cells to identify compounds that modulate LPR5 (Group VI) combined with a search for modulators that modulate LPR5 (Group VII) would not be undue. Applicant's argument is not persuasive. A search for the methods steps does not require searching the modulator, as the method does not necessarily result in finding a compound that modulates LPR5 function. A search for the modulator does not result in finding the method steps because the modulator may be found using a transgenic animal.

The requirement is still deemed proper and is therefore made FINAL.

Claim 1-4 and 13-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

Claims 5-12 are under consideration in the instant office action.

Claim Objections

Claim 10 is objected to because it is dependent upon claim 1 which is not under consideration.

Specification

The disclosure is objected to because of the following informalities: pg 50, line 18 and 21 refer to retinal regeneration in context of retinal degeneration on line 20. Retinal

regeneration is not a species of retinal degeneration. An animal cannot have both retinal regeneration and retinal degeneration. Clarification is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in th art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

1) A transgenic mouse whose genome comprises a homozygous disruption of LPR5, wherein said mouse lacks functional LPR5 and wherein said mouse has a phenotype of retinal degeneration,

2) A method of making a transgenic mouse having a disruption of LPR5 comprising i) obtaining a mouse ES cell having a disruption of LPR5, ii) introducing said ES cell into a mouse blastocyst, iii) implanting said blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and iv) breeding said chimeric mouse to produce a transgenic mouse whose genome comprises a homozygous disruption of LPR5, wherein said mouse lacks functional LPR5 and wherein said mouse has a phenotype of retinal degeneration, and

3) A cell whose genome comprises a homozygous disruption of LPR5 isolated from a transgenic mouse whose genome comprises a homozygous disruption of LPR5,

wherein said mouse lacks functional LPR5 and wherein said mouse has a phenotype of retinal degeneration,

does not reasonably provide enablement for any animal, LPR5 gene, phenotype, cell, disruption, method of making a transgenic or method of using a transgenic as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 8 is directed toward a transgenic non-human animal having a disruption in an LPR5 gene.

The specification does not enable a transgenic as claimed with a wild-type phenotype. The transgenics throughout the claims do not recite any phenotype and may, therefore, have any phenotype including wild-type phenotype. The specification does not provide any use for a transgenic having a disruption in LPR5 that has a wild-type phenotype. The only disclosed phenotype for the transgenic claimed is one that correlates to a mutation in LRP5 (pg 3, line 10). Therefore, claim 8 should recite a non-wild-type phenotype that correlates to a mutation in LRP5.

The specification does not enable any non-wild-type phenotype other than retinal degeneration. At the time of filing, one of skill in the art filing could not predict the phenotype of a knockout animal (Moreadith, 1997, J. Mol. Med., Vol. 75, pages 208-216; see page 208, column 2, last full paragraph; Aszodi et al., 1998, J. Molecular Med., Vol. 76, pages 238-252; see abstract). Leonard (1995, Immunological Reviews, Vol. 148, pages 98-113) disclosed mice with a disruption in the g_c gene, which were

intended to be a model for X-linked severe combined immunodeficiency (XSCID), but display a variety of unexpected traits (abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, line 7). Moens (1993, Development, Vol. 119, pages 485-499) disclosed that two mutations produced by homologous recombination in two different locations of the N-myc gene produce two different phenotypes in mouse ES cells, one leaky and one null (see abstract). The individual gene of interest and sequences present in the knockout construct are important factors in determining the phenotype of the knockout (Wall, 1996, Theriogenology, Vol. 45, pages 57-68; paragraph bridging pages 61-62). The specification teaches making a transgenic mouse whose genome comprises a homozygous disruption in the mouse LPR5 gene, wherein said mouse lacks functional LPR5 and has retinal degeneration (pg 50). For enablement purposes, it is assumed that "regeneration" on pg 50 should be "degeneration." The results of the open field testing in Fig. 4 and 5 and pg 51 do not correlate to a phenotype because "possible increased anxiety" and "significant hypoacitivity" (lines 4 and 7 of pg 51) are not specific to any disease and are not statistically significant because the number of mice tested is not disclosed and the difference observed is not significant. In fact, it cannot be determined what the "2,1," means in "2,1,-/-,Male" or "2,1,+/+,Male" in Fig. 4 and 5. Given the unpredictability in the art taken with the guidance provided in the specification, it would have required one of skill in the art undue experimentation to

determine the phenotype of a knockout other than retinal degeneration. Therefore, claim 8 should be limited to transgenics having a phenotype of retinal degeneration.

The specification does not teach how to make animals having a disruption in an LPR5 gene other than mice. The state of the art at the time of filing was such that embryonic stem (ES) cell technology had only been successful in mice. Wagner (May 1995, Clin. and Experimental Hypertension, Vol. 17, pages 593-605) and Mullins (1996, J. Clin. Invest., Vol. 98, pages S37-S40) taught germline transmission of ES cells has not been demonstrated in species other than mice and the growth of ES cells from species other than mice is unreliable. Wall (1996, cited above) taught transgene expression and the physiological result of such expression in livestock was not always accurately predicted in transgenic mice (page 62, line 7). The specification fails to provide sufficient guidance to make transgenics other than mice by teaching obtaining ES cells in species other than mice. The specification does not teach the nucleic acid sequence of the LPR5 gene in non-mice, non-human species or correlate the LPR5 gene in mice to the LPR5 gene in other species. The specification does not teach how to make knockout animals other than mice or correlate making knockout mice to other species. Therefore, the specification does not provide adequate guidance for one of skill in the art to make a transgenic, non-human animal in any species other than mice.

If the specification did teach how to make transgenics in species other than mice, the specification does not provide adequate correlation between the phenotype obtained in mice to the phenotype obtained in other species. The state of the art at the time of filing was that the phenotype of transgenic mice does not predict the phenotype

in non-mice species. Models of human diseases have relied on transgenic rats when the development of transgenic mice having the desired phenotype was not feasible. Mullins (1990, Nature, Vol. 344, pg 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse Ren-2 renin transgene. Hammer (1990, Cell, Vol. 63, pg 1099-1112) describe spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human b_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins, 1989, EMBO, Vol. 8, pg 4065-4072; Taurog, 1988, J. Immunol., Vol. 141, pg 4020-4023) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats. Therefore, the specification does not enable making transgenic having retinal degeneration in species other than mice.

Claims 5-7 are directed toward cells having a disruption in an LRP5 gene. Claims 6 and 7 are limited to a murine cells. Claim 7 is limited to murine ES cells. "Murine" encompasses mice and rats (http://www.m-w.com/cgi-bin/dictionary?book=Dictionary&va=murine). Claim 9 is directed toward a cell derived from the transgenic of claim 8. The specification does not provide adequate guidance to make cells as broadly claimed using transgenic animal technology in species other than mice for reasons above. In particular, the specification does not teach how to make murine ES cells as broadly claimed because the specification does not teach rat ES cells or correlate mouse ES cells to rat ES cells. As such, claim 7 should be limited to mouse ES cells. The specification does not teach how to knockout the LRP5 gene in

non-ES cells or the nucleic acid sequence of non-mouse LRP5 genes. Without such guidance it would require one of skill in the art undue experimentation to make any cell having a disruption in LRP5 as broadly claimed. One of skill would have been limited to mouse ES cells and isolating cells from the transgenic of claim 8.

Claim 10 is directed toward a method of making a transgenic mouse having a disruption in LRP5 using a cell having a construct with two sequences of LRP5, introducing the cell into a blastocyst, implanting the blastocyst into a pseudopregnant mouse which gives birth to chimeric mice, and breeding the chimeric mouse to produce the transgenic mouse. The claim does not require using mouse cells or blastocysts which is considered essential to the invention. The claim does not require using ES cells which is the only type of cell taught in the specification that can be introduced into a blastocyst and result in a chimeric mouse as claimed. The claim does not require a phenotype which is required for reasons cited above. Given the unpredictability in the art taken with the guidance provided in the specification, the cell in a) should be a mouse ES cell, the blastocyst in b) should be a mouse blastocyst, and the transgenic mouse produced should have a genome comprising a homozygous disruption in LRP5, wherein said mouse lacks functional LRP5 and has retinal degeneration.

Claims 11 and 12 are directed toward methods of screening compounds that modulate LRP5 expression and function, respectively, using a transgenic. Claim 11 does not have a disclosed purpose because the

transgenic does not express LRP5; therefore, expression of LRP5 cannot be determined as in step (c). Step (c) in either claim requires determining whether the expression or function of LRP5 is modulated but does not recite how to make such a determination, and the specification does not teach how to make such a determination. Nor does the specification teach any function of LRP5 that can be of use in the method. While the specification teaches transgenics having retinal degeneration, the specification does not teach how to determine whether a compound modulates retinal degeneration. Such a disclosure is essential to determine compounds that modulate LRP5 expression or function as claimed. What is required is a disclosure of the controls used, how to compare the transgenic animal to the control and when to test for expression and/or function. Without such a disclosure, the specification does not provide adequate guidance for one of skill to make the comparison required to determine compounds that modulate LRP5 expression or function. Finally, the claims should be limited to using transgenic mice whose genomes comprise a homologous disruption in LRP5, wherein said mice lack functional LRP5 and have retinal degeneration for reasons cited above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 5-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Rohlmann (1998, J. Clin. Invest., Vol. 101, pg 689-695).

Rohlmann taught making a transgenic mouse having a disruption in LRP made using ES cells (pg 690, col. 1, first full para.). Since the patent office does not have the means to sequence and determine which LRP gene was disrupted by Rohlmann, without evidence to the contrary, Rohlmann disrupted the LRP5 gene as claimed. Rohlmann taught administering adenovirus to the mice and determining the effect on the mice which is equivalent to the methods of claims 11 and 12.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rohlmann (1998, J. Clin. Invest., Vol. 101, pg 689-695) in view of Hey (1998, Gene, Vol. 216, pg 103-111).

Rohlmann taught making a transgenic mouse having a disruption in LRP made using ES cells (pg 690, col. 1, first full para.). Rohlmann did not

teach the LRP gene was LRP5 as claimed. Rohlmann taught administering adenovirus to the mice and determining the effect on the mice which is equivalent to the methods of claims 11 and 12.

However, Hey taught the nucleic acid sequence of the mouse LRP5 gene (pg 107).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a transgenic mouse having a disruption in LRP as taught by Rohlmann wherein the LRP was LRP5 as taught by Hey. One of ordinary skill in the art at the time the invention was made would have been motivated to disrupt the LRP5 gene because Rohlmann taught disrupting LRP genes. One of ordinary skill in the art at the time the invention was made would have been motivated to use the method of Rohlmann to disrupt LRP5 because Hey taught LRP5 is expressed in the liver (pg 108, para. Bridging col. 1-2; Fig. 5A, lane 5) and Rohlmann taught inhibiting expression of LRP specifically in the liver (pg 689, last para.). One of ordinary skill in the art at the time the invention was made would have been motivated to make an LRP5 knockout to determine the function of LRP5 in the liver.

Thus, Applicants' claimed invention, as a whole is prima facie obvious in the absence of evidence to the contrary.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Kato (2002, J. Cell Biol., Vol. 167, Pg 303-314) taught transgenic mice having a disruption in LRP5 had osteoblast proliferation, osteopenia and embryonic eye vascularization (see entire article) which is not disclosed in the instant application. Kato did not teach the mice had retinal degeneration or anxiety as described in the instant application.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL C. WILSON
PATENT EXAMINER

Application No.: 09/887540

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: The sequence in Fig. 3A does not have a SEQ ID NO. If it part of SEQ ID NO:1 continued in Fig. 3B, clarification is required in the Figure or in the description of Fig. 3A-3B.

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

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